

## Viewpoint

# Compliance in clinical trials

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**SUMMARY** Compliance with treatment can be an important determinant of the outcome of clinical trials. To date there is no completely satisfactory method of measuring compliance and some of the most widely used methods are inadequate. The various methods of measuring compliance and how they have been applied to clinical trials are described, and improvements in the standard of the measurement and reporting of compliance in clinical trials are suggested.

Poor compliance is a major problem in medical practice.<sup>1-3</sup> In the broadest sense it can refer to any deviation in the patient's behaviour from that recommended by the doctor, including such areas as dietary advice, advice on smoking, or even advice about attendance for further investigation or follow up. The term 'poor compliance' can imply failure of the patient to follow the doctor's advice because of communication problems, 'forgetfulness', or a volitional act of the patient. In common usage the term compliance usually refers to the patient's adherence to prescribed drugs and in this sense the end result of poor or inadequate compliance for whatever reason is the patient's failure to ingest prescribed drugs.

Poor compliance with prescribed drugs can also jeopardise the outcome of clinical trials by reducing their power. It has been calculated that if 30% of patients in a clinical trial had inadequate compliance then double the number of patients would need to be studied to produce a study with the same  $\alpha$  and  $\beta$  values.<sup>4</sup> The situation is further complicated by the fact that in a comparative study the clinical effect of the same level of incomplete compliance may vary with different drugs. For instance, for two drugs normally prescribed to be taken once daily the omission of one dose of a sustained release preparation of a short half life drug may result in ineffective circulating concentrations of that drug for most of the day, whereas omission of a single dose of a long half life drug will have relatively little effect on

circulating concentrations. Although it is sometimes possible to identify individual patients with very poor compliance, for instance by a marked improvement in disease control with supervised administration of oral drugs as an inpatient,<sup>5</sup> it is much more difficult to measure compliance in groups of patients such as those participating in clinical trials. The methods traditionally used for measuring compliance in this situation are far from adequate and all of those methods overestimate compliance. Table 1 summarises the available methods of measuring compliance.

### Studies of compliance with antirheumatic drugs

A number of compliance studies with antirheumatic drugs have been carried out using most of the currently available methods of assessing compliance. Deyo *et al*, using 'medication refills' to measure compliance, found that more than 50% of patients taking prednisone and over 80% of patients taking aspirin obtained 80% or less of the necessary number of refills to ensure continuous treatment over six months.<sup>25</sup> These authors also looked at compliance with penicillamine and a number of non-steroidal anti-inflammatory drugs (NSAIDs) and attempted to relate compliance to diagnosis. These data, however, are very difficult to interpret as they describe the mean compliance for each drug. A mean compliance with penicillamine of 84.4% could imply that at the extremes 15% of patients took no treatment and the rest had 100% compliance or that all patients took 84.4% of their tablets, two patterns of compliance which could have totally different

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effects on the outcome of treatment. An interview based comparison of compliance with diclofenac 25 mg four times a day and diclofenac 100 mg sustained release once daily found that almost twice the total quantity of drug was missed on the first regimen compared with the once daily preparation.<sup>26</sup> One study of 123 patients attending a rheumatology clinic attempted to classify compliance with drug treatment into 'full' and 'partial/poor' using the impression of the physician, who also had access to blood salicylate measurements. These authors classified 78 (63%) as having full compliance.<sup>12</sup> A recent community based study using interview found that 63.5% of 178 patients with rheumatoid arthritis claimed that they did not alter their dose of drugs from that instructed.<sup>27</sup> Recently we examined compliance, using a pharmacological marker (low dose phenobarbitone), in 26 rheumatoid patients who had shown a poor response to high doses of D-penicillamine and found incomplete compliance in 11 (42%), only one of whom could be identified by interview, six by return tablet count, and six by clinician's impression.<sup>6</sup> The

definition of inadequate compliance in this study was determined to give patients the 'benefit of the doubt' and probably, in fact, many more of these patients had incomplete compliance.

### Patterns of compliance and their possible impact on clinical trials

The various methods used to measure compliance may result in different estimates of compliance. This is best illustrated by the results of two studies of compliance by children given phenoxymethylpenicillin for streptococcal sore throat, one of which found that 83% of children had stopped treatment by day 9,<sup>28</sup> whereas the other found that 89% of children were still taking the drug on day 9 or 10.<sup>29</sup>

The studies described in the previous section span three continents and two decades and use different classifications of compliance. Despite this, and even though all the methods are likely to overestimate compliance, it is clear that the extent of poor compliance with antirheumatic drugs is a problem of some magnitude. Based on the results of published

Table 1 *Methods of measuring compliance*

<i>Method</i>	<i>Advantages</i>	<i>Disadvantages</i>
Clinician's impression <sup>6-8</sup>	Quick and easy	Very unreliable; physicians unable to estimate compliance any more accurately than they might have done by chance
Assessment of pharmacological response <sup>5,9</sup>	Easy with some drugs	Limited applicability. Not reliable as there is not always a straightforward link between compliance and clinical outcome
Checking prescription records/refills <sup>10,11</sup>	Relatively easy	Collection of prescription(s) does not necessarily mean that tablets have been taken
Patient interview <sup>8,12,13</sup>	Quick and easy. Patients who admit to poor compliance are often telling the truth	Patients usually overestimate their compliance
Residual tablet count/return bottle count <sup>14-16</sup>	Cheap and easy. May be useful in detecting poor compliance if an excess of tablets is returned	Tablets removed from the bottle are not necessarily ingested. Easily open to manipulation; patients may forget to return tablets or bring back empty bottles
Use of devices to monitor removal of tablets from container <sup>17,18</sup>	Less open to manipulation than the residual tablet count	Removal of doses does not guarantee ingestion
Assay of therapeutic drugs in blood or urine <sup>13,19,20</sup>	More objective method of assessing compliance	Many drugs have unsuitable pharmacokinetics, with extensive interindividual variation or short half lives, or both. Assays may not be readily available. Control data may not be available
Use of a pharmacological marker with a short half life ( $t_{1/2}$ ), e.g. riboflavin, isoniazid <sup>15,21,22</sup>	More objective method of assessing compliance. Widely applicable	Short $t_{1/2}$ markers indicate compliance only at time of sampling*
Use of a pharmacological marker/indicator with a long half life, e.g. minimal doses of phenobarbitone, digoxin, bromide <sup>16,23,24</sup>	Widely applicable. Can provide a more quantitative measure of compliance. Less open to manipulation than short $t_{1/2}$ markers. Can indicate compliance over a longer period (weeks) before sampling	Do not indicate compliance over short dosage intervals (e.g. whether a drug has been taken every 6 to 8 hours)*

\*Also require formulation/encapsulation with therapeutic drug; may be a need to exclude effect on bioavailability. Ethical implications need to be considered.

studies, including studies of our own using an indicator of compliance in different therapeutic areas,<sup>30-35</sup> our personal experience and that of colleagues and friends while taking tablets, and on our clinical experience, we have produced an outline of what we feel are the most likely patterns of compliance with long term treatment (Table 2).

In relation to clinical trials of longer term treatment the two most important groups may be those who take little or none of their treatment and, because of its size, those with sloppy compliance. Many doctors will recognise themselves as falling into the last category. Failure in clinical trials to detect those patients with low levels of compliance may result in an underestimate of the efficacy of the treatment, especially if the comparative treatment is placebo. In one study it was calculated that the statistical outcome of a trial would change from 'non-significant' to 'significant' depending on whether or not a single patient with poor compliance was included.<sup>36</sup> Sloppy compliance may also be very important. The omission of every third or fourth dose is probably common, particularly with three or four times a day regimens and among busy younger patients. Even if the level of compliance is equal in all the treatment groups, differences in formulation, pharmacokinetics, or dose scheduling may result in the relative impact of poor compliance varying widely with different drugs. Thus poor compliance may introduce a bias in favour of drugs with long half lives or flat dose-response curves, or both. It has been claimed that just such a bias occurred in a major trial comparing ranitidine with cimetidine.<sup>37 38</sup>

It is argued that the pattern of compliance in 'intention to treat' trials reflects compliance in everyday practice and that compliance as a factor affecting outcome can be disregarded in these trials.<sup>39</sup> The trial design (frequency of follow up visits, return tablet counts, blood sampling, etc) and the clinician's attitude (for example, enthusiasm),

however, may provide a different pattern of compliance from routine practice. Furthermore, knowing the efficacy of drugs in those patients with good compliance could be important in the development of new treatments. Either it might be possible to produce strategies to improve compliance or a formulation could be used which would minimise the impact of sloppy compliance. Incomplete compliance may also be important in trials which attempt to relate either response or toxicity to other factors, such as HLA genotype.

### Current practices in measuring and reporting compliance in clinical trials

Ten years ago it was pointed out that compliance is seldom discussed in reports of clinical trials and that even when it is considered compliance data are often handled inappropriately.<sup>40</sup> Some recent trials of antirheumatic drugs have made no attempt to assess compliance. Despite the lack of any stated formal attempt to measure compliance one study mentions three patients who discontinued treatment because of non-compliance.<sup>41</sup> Many studies have attempted to assess compliance by return tablet count or interview, or both, but have made no attempt to define inadequate compliance and report their results in the broadest of terms—for example, 'based on pill counts there were no significant violations of the protocol',<sup>42</sup> 'the effect of non-compliance did not significantly alter the results'.<sup>43</sup> One study which assessed compliance using return tablet count reported the results in an exemplary fashion, giving the percentage of patients falling within each band of compliance. Although 7.5% of patients had <70% compliance as assessed by this method, however, no mention was made as to how this was dealt with in the handling of the data on efficacy and toxicity.<sup>44</sup> Other trials which attempted to assess compliance by interview or return tablet count report only a very low level of incomplete com-

Table 2 *Patterns of compliance during long term treatment*

Compliance	Proportion of treatment taken (%)	Probable proportion of patients (%)	Efficacy of the drug treatment
'Scrupulous'	90-109	10-40*	Unimpaired
'Sloppy'	60-89	30-70*	May be impaired or unimpaired, depending on the drug in question and the condition being treated (see text)
Consistently low	30-59	1-5**	Usually impaired**
Virtually nil	0-29	5-20	Almost always impaired**

\*The size of these groups may vary substantially with the condition, patient group, drug, and dosage regimen in question.

\*\*This table refers to long term treatment. There may be many more patients who take half or one third of a short course—for example, antibiotic treatment, and in those circumstances even a few doses may occasionally be effective.

pliance detected.<sup>45-47</sup> Other drug studies have measured plasma concentrations of the therapeutic drug either with<sup>48</sup> or without<sup>49, 50</sup> specific reference to compliance. Statements are then made about compliance, however, without mention of the pharmacokinetics of the drug or the expected concentrations at steady state.<sup>48</sup> Similarly, studies sometimes measure a pharmacodynamic effect of the drug without giving any information about the dose-response relation of this effect or, in fact, the kinetics of the effect itself.<sup>51</sup>

Other problems which have been noted from outwith rheumatology are the use of a ratio of parent drug to metabolite taken in isolation with no details of control values for the drug, the metabolite, or the ratio<sup>19</sup> or the comparison of compliance with different drugs using, in each case, urine tests for the presence of the therapeutic drug.<sup>20</sup> Not surprisingly this last study found that the incidence of positive urine tests varied directly with the half life of the drug. Even a trial which went to the trouble of labelling five year supplies of gemfibrozil for 4000 patients with minimal doses of digoxin in an attempt to monitor compliance failed to give adequate information on how the results were interpreted.<sup>52</sup> A final approach is to try to ensure complete compliance. The level of effort and, one assumes, success in achieving this varies from the bland unsupported statement that 'at each centre the office assistant ensured patient compliance'<sup>53</sup> to making sure that each dose is witnessed or given by the investigator.<sup>54</sup>

### What can be done?

The current situation on compliance and clinical trial reporting seems somewhat analogous to the situation in statistics a decade or two ago, when a substantial proportion of reports used inappropriate statistical methods or gave inadequate details of the tests applied, or both. The first step in bringing compliance out of this dark age must be increased awareness among authors, reviewers, editors, and readers of both its importance and the problems with current methods of measurement. This awareness should result in a more appropriate use of some of the currently available methods of measuring compliance.

This increased awareness and use of compliance measurements should not lead to complacency about the current often inadequate methods but should act as a stimulus for further research to produce better methods. The 'Workshop on the development of markers for use as adherence measures', sponsored by the National Heart, Lung, and Blood Institute, highlighted 'adherence

markers' and 'devices for adherence evaluation' as the most likely ways forward.<sup>55</sup> Subsequent descriptions of such methods have been published and some have been used in clinical trials.<sup>52, 56</sup> None of these methods is perfect, however, and further refinement of individual methods, development of new methods, and evaluation of their combined use is necessary. For compliance measured within a clinical trial we make the following recommendations: (a) the limitations of any method used should be appreciated and discussed; (b) compliance should be described by placing patients into broad 'bands' of compliance with information being given on the number of patients in each band; (c) inadequate compliance should be defined in a way which is appropriate to the pharmacology of the drug under scrutiny and the method used to measure compliance. It should relate to a level of compliance in an individual at which the desired pharmacodynamic effects of the drug might be attenuated; (d) it should be stated in the protocol how data from patients who fulfil the criteria of inadequate compliance as designated in (c) will be handled in the analysis of results.

To use the analogy with statistics we do not expect that these proposals will lead us from the unsupported p values of 20 years ago to today's confidence intervals, power calculations, and odds ratios overnight, but hopefully they may stimulate a more rational approach to compliance in clinical trials.

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